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SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Natalie Davis Examiner #: 78962 Date: 6-5-01
Art Unit: 1642 Phone Number 308-6410 Serial Number: 09/730729
Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL
9E12 CM1 9B09

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): Simantov R
Silvestein, R

Earliest Priority Filing Date: 12-6-99

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

Please Search Claims 1-3.

Point of Contact:
Beverly Sheers
Technical Info. Specialist
CM1 12C14 Tel: 308-4994

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STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: Beverly 84994	NA Sequence (#) _____	STN Beverly ✓
Searcher Phone #: _____	AA Sequence (#) _____	Dialog _____
Searcher Location: _____	Structure (#) _____	Questel/Orbit _____
Date Searcher Picked Up: _____	Bibliographic _____	Dr.Link _____
Date Completed: 06-21-01	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: 12	Fulltext _____	Sequence Systems _____
Clerical Prep Time: _____	Patent Family _____	WWW/Internet _____
Online Time: 16	Other _____	Other (specify) _____

PTO-1590 (1-2000)

Davis, N.
09/730379

[redacted] ENTERED AT 09:53:50 ON 21 JUN 2001
E "HISTIDINE-RICH GLYCOPROTEIN"/CN
L1 3 S "HISTIDINE-RICH GLYCOPROTEIN"?/CN
E THROMBOSPONDIN/CN
L2 36 S THROMBOSPONDIN ?/CN

[redacted] ENTERED AT 09:54:42 ON 21 JUN 2001
L1 3 SEA FILE=REGISTRY ABB=ON PLU=ON "HISTIDINE-RICH GLYCOPROTEIN"?/CN
L2 36 SEA FILE=REGISTRY ABB=ON PLU=ON THROMBOSPONDIN ?/CN
L3 336 SEA FILE=CAPLUS ABB=ON PLU=ON L1 OR HRGP OR HISTIDINE(W)RICH(W)(GP OR GLYCOPROTEIN OR GLYCO PROTEIN)
L4 14 SEA FILE=CAPLUS ABB=ON PLU=ON L3 AND (L2 OR THROMBOSPONDIN OR THROMBO SPONDIN)

L4 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:125729 CAPLUS
DOCUMENT NUMBER: 134:293853
TITLE: Genetic screening of candidate genes for a prothrombotic interaction with type I protein C deficiency in a large kindred
AUTHOR(S): Scott, Bruce T.; Bovill, Edwin G.; Callas, Peter W.; Hasstedt, Sandra J.; Leppert, Mark F.; Valliere, Julia E.; Varvil, Tena S.; Long, G. L.
CORPORATE SOURCE: Department of Pathology, University of Vermont, Burlington, VT, 05405, USA
SOURCE: Thromb. Haemostasis (2001), 85(1), 82-87
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: F. K. Schattauer Verlagsgesellschaft mbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The incomplete penetrance of thrombosis in familial protein C deficiency suggests disease occurs when this deficit is combined with addnl. abnormalities in the hemostatic system. The pattern of inherited thrombophilia in the Vermont II kindred, which is affected by a clin. dominant type I protein C deficiency, provides strong evidence for a second unidentified gene that segregates independently of protein C deficiency and increases susceptibility to thrombosis. To test the second gene hypothesis, thirty-four candidate genes for proteins involved in hemostasis or inflammation were tested as the unknown defect, using highly polymorphic short tandem repeat (STR) markers in an informative subset of the kindred. The genes considered are; .alpha.-fibrinogen, .beta.-fibrinogen, .gamma.-fibrinogen, prothrombin, tissue factor, factor V, protein S, complement component 4-binding protein, factor XI, factor XII, factor XIIIa, factor XIIIb, **histidine-rich glycoprotein**, high-mol.-wt. kininogen, kallikrein, von Willebrands factor, platelet factor 4, **thrombospondin**,

antithrombin III, .alpha.-1-antitrypsin, thrombomodulin, plasminogen, tissue plasminogen activator, urokinase plasminogen activator, plasminogen activator inhibitor-1, plasminogen activator inhibitor-2, protein C inhibitor, .alpha.-2-plasmin inhibitor, kallistatin, lipoprotein a, interleukin 6, interleukin 1, cystathionine-.beta.-synthase, and methylenetetrahydrofolate reductase. Mutations in many of these genes have been previously established as independent risk factors for thrombosis. However, linkage anal. provided no evidence to implicate any of the candidate genes as the second inherited factor that promotes thrombophilia in this kindred.

REFERENCE COUNT: 54

REFERENCE(S):
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(5) Bovill, E; Thromb Haemost 2000, V83, P366 CAPLUS
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(9) Collins, A; Proc Natl Acad Sci (USA) 1996, V93, P14771 CAPLUS
(10) De Stefano, V; Blood 1996, V87(9), P3531 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:20739 CAPLUS

DOCUMENT NUMBER: 134:191487

TITLE: **Histidine-rich glycoprotein** inhibits the antiangiogenic effect of **thrombospondin**-1

AUTHOR(S): Simantov, Ronit; Febbraio, Maria; Crombie, Rene; Asch, Adam S.; Nachman, Ralph L.; Silverstein, Roy L.

CORPORATE SOURCE: Division of Hematology-Oncology, Department of Medicine, Weill Medical College of Cornell University, New York, NY, 10021, USA

SOURCE: J. Clin. Invest. (2001), 107(1), 45-52
CODEN: JCINAO; ISSN: 0021-9738

PUBLISHER: American Society for Clinical Investigation

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Angiogenesis is crit. for the growth and proliferation of tumors as well as for normal development. The authors now describe a novel role for **histidine-rich glycoprotein** (**HRGP**) in the modulation of angiogenesis. **HRGP** is a plasma protein that circulates in relatively high concns. (1.5 .mu.M), but has no known function in vivo. The authors have shown previously that **HRGP** binds with high affinity to **thrombospondin**-1 (TSP-1), a homotrimeric glycoprotein that

is a potent inhibitor of angiogenesis. The antiangiogenic activity of TSP-1 is mediated by the binding of properdin-like type I repeats to the receptor CD36. The authors found that binding of **HRGP** to TSP-1 was similarly mediated by TSP type I repeats. **HRGP** colocalized with TSP-1 in the stroma of human breast cancer specimens, and this interaction masked the antiangiogenic epitope of TSP-1. In assays performed in vitro of endothelial cell migration and tube formation, and in vivo corneal angiogenesis assays, **HRGP** inhibited the antiangiogenic effect of TSP-1. These studies suggest that **HRGP** can modulate the antiangiogenic activity of TSP-1, and identify a potential mechanism of resistance to the antiangiogenic effect of TSP-1.

REFERENCE COUNT: 41

REFERENCE(S):
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(4) Borza, D; J Biol Chem 1997, V272, P5718 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:325360 CAPLUS
DOCUMENT NUMBER: 133:146523

TITLE: **Thrombospondin**-1 binds to polyhistidine with high affinity and specificity

AUTHOR(S): Vanguri, Vijay K.; Wang, Shuxia; Godyna, Svetlana; Ranganathan, Sripriya; Liau, Gene
CORPORATE SOURCE: Department of Vascular Biology, Jerome H. Holland Laboratory, Rockville, MD, 20855, USA

SOURCE: Biochem. J. (2000), 347(2), 469-473
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Thrombospondin**-1 (TSP1) is a secreted trimeric glycoprotein of 450 kDa with demonstrated effects on cell growth, adhesion and migration. Its complex biol. activity is attributed to its ability to bind to cell-surface receptors, growth factors and extracellular-matrix proteins. In this study, we used a 125I solid-phase binding assay to demonstrate that TSP1 binds specifically to proteins contg. polyhistidine stretches. Based on studies with three different six-histidine-contg. recombinant proteins, we derived an av. dissocn. const. of 5 nM. The binding of 125I-labeled TSP1 to these proteins was inhibited by peptides contg.

histidine residues, with the degree of competition being a function of the no. of histidines within the peptide. Binding was not inhibited by excess histidine or imidazole, indicating that the imidazole ring is not sufficient for recognition by TSP1. Heparin was a potent inhibitor of binding with a Ki of 50 nM, suggesting that the heparin-binding domain of TSP1 may be involved in this interaction. This was confirmed by the ability of a recombinant heparin-binding domain of TSP1 to directly compete for TSP1 binding to polyhistidine-contg. proteins. Affinity chromatog. with a polyhistidine-contg. peptide immobilized on agarose revealed that TSP1 in platelet releasates is the major polypeptide retained on the six-histidine-peptide column. We conclude that TSP1 contains a high-affinity binding site for polyhistidine and this is likely to be the mol. basis for the obsd. binding of TSP1 to **histidine -rich glycoprotein**. The possibility that other polyhistidine-contg. proteins also interact with TSP1 warrants further study.

REFERENCE COUNT: 43

REFERENCE(S):
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(2) Alexander, R; Biochem J 1984, V217, P67 CAPLUS
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(5) Dixit, V; J Biol Chem 1984, V259, P10100 CAPLUS
(6) Dixit, V; J Biol Chem 1986, V261, P1962 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:795994 CAPLUS
DOCUMENT NUMBER: 132:31744
TITLE: Gene probes used for genetic profiling in healthcare screening and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Ltd., UK
SOURCE: PCT Int. Appl., 745 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964627	A2	19991216	WO 1999-GB1780	19990604

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU,

CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW,
AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

GB 1998-12099	A	19980606
GB 1998-13291	A	19980620
GB 1998-13611	A	19980624
GB 1998-13835	A	19980627
GB 1998-14110	A	19980701
GB 1998-14580	A	19980707
GB 1998-15438	A	19980716
GB 1998-15574	A	19980718
GB 1998-15576	A	19980718
GB 1998-16085	A	19980724
GB 1998-16086	A	19980724
GB 1998-16921	A	19980805
GB 1998-17097	A	19980807
GB 1998-17200	A	19980808
GB 1998-17632	A	19980814
GB 1998-17943	A	19980819

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic.RTM." profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate

healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

L4 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:795993 CAPLUS
DOCUMENT NUMBER: 132:31743
TITLE: Gene probes used for genetic profiling in healthcare screening and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Limited, UK
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964626	A2	19991216	WO 1999-GB1779	19990604
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9941586	A1	19991230	AU 1999-41586	19990604
AU 9941587	A1	19991230	AU 1999-41587	19990604
GB 2339200	A1	20000119	GB 1999-12914	19990604
EP 1084273	A1	20010321	EP 1999-925207	19990604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.:

GB 1998-12098	A	19980606
GB 1998-28289	A	19981223
GB 1998-16086	A	19980724
GB 1998-16921	A	19980805
GB 1998-17097	A	19980807
GB 1998-17200	A	19980808
GB 1998-17632	A	19980814
GB 1998-17943	A	19980819

WO 1999-GB1779 W 19990604

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.

L4 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:38194 CAPLUS
DOCUMENT NUMBER: 130:194856
TITLE: Interaction of recombinant procollagen and properdin modules of **thrombospondin**-1 with heparin and fibrinogen/fibrin
AUTHOR(S): Panetti, Tracee Scalise; Kudryk, Bohdan J.; Mosher, Deane F.
CORPORATE SOURCE: Departments of Medicine and Biomolecular Chemistry, University of Wisconsin, Madison, WI, 53706, USA
SOURCE: J. Biol. Chem. (1999), 274(1), 430-437
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Many properties have been assigned to the procollagen and properdin (Type I) modules of **thrombospondin**-1 (TSP1) based on activities of large proteolytic fragments of TSP1 or peptides contg. TSP1-derived sequences. To examine the activities of the modules more exactly, we expressed the first properdin module (P1); the third properdin module (P3); the first and second properdin modules (P12); the first, second, and third properdin modules (P123); and the procollagen module with the first, second, and third properdin modules (CP123) in the GELEX expression vector (GE1) using the baculovirus system. GE1 encodes the pre-pro sequence, the transglutaminase crosslinking site(s), the protease-sensitive site,

and the gelatin binding domain from the amino terminus of rat fibronectin. All five recombinant proteins were expressed by insect cells, secreted into the culture medium, and purified by gelatin-agarose affinity chromatog. P123 shared with TSP1 a resistance to trypsin unless reduced and alkylated. P12/GE1, P123/GE1, and CP123/GE1 bound poorly to heparin-agarose except in the absence of sodium chloride, whereas peptides based on P2 are known to bind to heparin in up to 150 mM sodium chloride. In crosslinking expts. employing activated recombinant factor XIII and the transglutaminase crosslinking site in the fibronectin-derived sequence, P12/GE1, P123/GE1, CP123/GE1, and P3/GE1 but not P1/GE1 became incorporated into a fibrin clot more than GE1 alone. Anal. of the complex indicated that crosslinking was to the portion of the fibrin .alpha.-chain remaining in the D-dimer of plasmin digests. P123 also cross-linked to the A.alpha.-chain of unclotted fibrinogen. P123 competed for 125I-TSP1 incorporation into the fibrin clot. P123 did not crosslink to plasminogen, **histidine-rich glycoprotein**, fibronectin, or plasma globulins other than fibrinogen/fibrin. These results indicate that the properdin modules of TSP1 specifically interact with fibrinogen/fibrin but not with heparin under physiol. conditions.

REFERENCE COUNT: 61

REFERENCE(S):

(1) Asakura, S; J Cell Biol 1992, V116, P465 CAPLUS
(2) Asch, A; Science 1993, V262, P1436 CAPLUS
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(5) Bacon-Baguley, T; J Biol Chem 1990, V265, P2317 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:266618 CAPLUS
DOCUMENT NUMBER: 120:266618
TITLE: Interaction of immobilized unfractionated and LMW heparins with proteins in whole human plasma
AUTHOR(S): Zammit, Adrian; Pepper, Duncan S.; Dawes, Joan
CORPORATE SOURCE: Heart Res. Inst., Sydney, 2050, Australia
SOURCE: Thromb. Haemostasis (1993), 70(6), 951-8
CODEN: THHADQ; ISSN: 0340-6245
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The profile of proteins bound to immobilized heparins in hirudin-anticoagulated human plasma was analyzed. In molar terms, antithrombin III was the most abundant protein bound to therapeutic

doses of unfractionated heparin (Mr = 12,000), whereas heparin cofactor II constituted <1% of the protein bound. **Histidine -rich glycoprotein** was the only plasma protein likely to influence anticoagulant activity by direct competition with antithrombin III, though significant quantities of complement Factor H, fibrinogen, fibronectin, vitronectin and apolipoprotein B were also detected. Only traces of von Willebrand factor, complement factor I, inter-.alpha.-trypsin inhibitor, .alpha.2-macroglobulin, serum amyloid P and transferrin were identified, and neither **thrombospondin** nor platelet factor 4 were measurable. Binding of both antithrombin III and **histidine-rich glycoprotein** varied with the ratio of heparin to plasma. Clexane (Mr = 4,500) also bound antithrombin III, but both **histidine-rich glycoprotein** and vitronectin were quant. significant neutralizing proteins. Neutralizing proteins dominated the binding profile for Oligo H (Mr = 2,200).

L4 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:52475 CAPLUS
DOCUMENT NUMBER: 118:52475
TITLE: **Thrombospondin**-derived hexapeptide and its uses
INVENTOR(S): Nachman, Ralph L.; Asch, Adam S.
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9217499	A1	19921015	WO 1992-US2825	19920407

W: JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE
PRIORITY APPLN. INFO.: US 1991-680710 19910408

AB The title hexapeptide has the sequence Cys-Ser-Val-Thr-Cys-Gly. The peptides may be used for inhibition of malarial adhesion or for inhibition of tumor cell metastasis. When inoculation of Plasmodium berghii sporozoites was preceded by incubation with antibodies to the hexapeptide of the invention, 60% of tested mice demonstrated a latency of 24 h when compared to the control group. The hexapeptide inhibited binding of **thrombospondin** to U937 cells. Prepn. of antibodies to the hexapeptide are described.

L4 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1989:130749 CAPLUS
DOCUMENT NUMBER: 110:130749
TITLE: Molecular modeling of protein-glycosaminoglycan interactions
AUTHOR(S): Cardin, Alan D.; Weintraub, H. J. R.
CORPORATE SOURCE: Merrell Dow Res. Inst., Cincinnati, OH, 45215, USA
SOURCE: Arteriosclerosis (Dallas) (1989), 9(1), 21-32
CODEN: ARTRDW; ISSN: 0276-5047
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Forty-nine regions in 21 proteins were identified as potential heparin-binding sites based on the sequence organizations of their basic and nonbasic residues. Twelve known heparin-binding sequences in vitronectin, apolipoproteins E and B-100, and platelet factor 4 were used to formulate 2 search strains for identifying potential heparin-binding regions in other proteins. Consensus sequences for glycosaminoglycan recognition were detd. as [-X-B-B-X-B-X-] and [-X-B-B-B-X-X-B-X-] where B is the probability of a basic residue and X is a hydropathic residue. Predictions were then made as to the heparin-binding domains in endothelial cell growth factor, purpurin, and antithrombin-III. Many of the natural sequences conforming to these consensus motifs show prominent amphipathic periodicities having both .alpha.-helical and .beta.-strand conformations as detd. by predictive algorithms and CD studies. The heparin-binding domain of vitronectin was modeled and formed a hydrophilic pocket that wrapped around and folded over a heparin octasaccharide, yielding a complementary structure. It is suggested that these consensus sequence elements form potential nucleation sites for the recognition of polyanions in proteins and may provide a useful guide in identifying heparin-binding regions in other proteins. The possible relevance of protein-glycosaminoglycans interactions in atherosclerosis is discussed.

L4 ANSWER 10 OF 14 CAPLUS
ACCESSION NUMBER: 1987:631724 CAPLUS
DOCUMENT NUMBER: 107:231724
TITLE: Binding of **thrombospondin** to immobilized ligands: specific interaction with fibrinogen, plasminogen, **histidine-rich glycoprotein**, and fibronectin
AUTHOR(S): Walz, Daniel A.; Bacon-Baguley, Theresa; Kendra-Franczak, Suzanne; DePoli, Patricia
CORPORATE SOURCE: Dep. Physiol., Wayne State Univ., Detroit, MI, 48201, USA
SOURCE: Semin. Thromb. Hemostasis (1987), 13(3), 317-25
CODEN: STHMBV; ISSN: 0094-6176

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Evidence was presented and discussed for the specific interaction of **thrombospondin** (TSP) with fibrinogen, plasminogen, **histidine-rich glycoprotein**, and fibronectin. Although the data are preliminary, a series of unique peptide sequence regions is believed to exist within the TSP mol., that will sep. direct the interaction of TSP with each of these ligands.

L4 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1986:474845 CAPLUS
DOCUMENT NUMBER: 105:74845
TITLE: Tissue plasminogen activator and urokinase enhance the binding of plasminogen to **thrombospondin**
AUTHOR(S): Silverstein, Roy L.; Harpel, Peter C.; Nachman, Ralph L.
CORPORATE SOURCE: Cornell Med. Cent., New York Hosp., New York, NY, 10021, USA
SOURCE: J. Biol. Chem. (1986), 261(21), 9959-65
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Thrombospondin** (TSP) is a multifunctional platelet .alpha.-granule and extracellular matrix glycoprotein that binds specifically to plasminogen (Plg) via that protein's lysine-binding site and modulates activation by tissue activator (TPA). In this study, the plasminogen activators, TPA and urokinase, are reported to greatly influence the binding of Plg to TSP. Using an ELISA and a TSP-Sepharose affinity bead-binding assay, it was found that Plg-TSP complex formation was markedly enhanced (up to 5-fold) when catalytic concns. of Plg activators were included in the reaction mixts. The enhancement was dependent upon the generation of small amts. of active plasmin and was duplicated by pretreatment of the immobilized TSP with plasmin prior to addn. of the Plg. The enhancement effect was assocd. with selective proteolysis of the immobilized TSP. Purified Lys-Plg (the plasmin modified form of native Glu-Plg) bound to TSP to a greater extent than did Glu-Plg, and binding of both forms was augmented by Plg activators. The apparent dissocn. consts. of complex formation were unchanged in the presence of Plg activators, suggesting that the enhancement effect was due to the generation of addnl. binding sites. The increased amt. of bound Plg was demonstrated to result in a similar increase in the amt. of plasmin generated from the complexes by TPA. Plg activators did not influence binding of Plg to **histidine-rich glycoprotein** or of **histidine-rich glycoprotein** to TSP, demonstrating

specificity. In addn., when TSP was treated with other proteases (human thrombin or human leukocyte elastase) no augmentation of Plg binding was seen. Thus, the initial prodn. of small amts. of plasmin from Plg immobilized on TSP in fibrin-free microenvironments could generate a pos. feedback loop by enzymically modifying both TSP and Plg, resulting in an increase in TSP-Plg complex formation leading to the localized prodn. of substantially more plasmin.

L4 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:537622 CAPLUS
DOCUMENT NUMBER: 103:137622
TITLE: Activation of immobilized plasminogen by tissue activator. Multimolecular complex formation
AUTHOR(S): Silverstein, Roy L.; Nachman, Ralph L.; Leung, Lawrence L. K.; Harpel, Peter C.
CORPORATE SOURCE: Cornell Med. Cent., New York Hosp., New York, NY, 10021, USA
SOURCE: J. Biol. Chem. (1985), 260(18), 10346-52
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ternary complex formation of tissue plasminogen activator (TPA) and plasminogen (Plg) with **thrombospondin** (TSP) or **histidine-rich glycoprotein** (**HRGP**) was demonstrated with an ELISA, an affinity bead assay, and a rocket immunoelectrophoresis assay. The formation of these complexes was specific, concn. dependent, saturable, lysine-binding site-dependent, and inhibitable by fluid-phase plasminogen. Apparent Kd values were .apprx.12-36 nM for the interaction of TPA with TSP-Plg complexes and 15-31 nM with **HRGP**-Plg complexes. At satn. the relative molar stoichiometry of Plg:TPA was 3:1 in TSP-contg. complexes and 1:1 in **HRGP**-contg. complexes. The activation of Plg to plasmin by TPA on TSP- and **HRGP**-coated surfaces was studied using a synthetic fluorometric plasmin substrate (D-Val-Leu-Lys-7-amino-4-trifluoromethylcoumarin). Kinetic anal. demonstrated a marked increase in the affinity of TPA for plasminogen in the presence of surface-assocd. TSP or **HRGP**. Compared to fluid-phase activation or activation on fibronectin- or Factor VIII-related antigen-coated surfaces, there was a 35-fold increase in efficiency of plasmin generation. A substantial amt. (.ltoreq.71%) of the plasmin formed remained surface-assocd. and was protected from inhibition by .alpha.2-plasmin inhibitor. A >200-fold increase in inhibitor concn. was required to effect 50% inhibition. Complex formation of locally released tissue plasminogen activator with Plg immobilized on TSP or **HRGP** surfaces may thus play an important role in effecting proteolytic events in nonfibrin-contg. microenvironments.

L4 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:449964 CAPLUS
DOCUMENT NUMBER: 103:49964
TITLE: Platelet **thrombospondin** forms a trimolecular complex with plasminogen and **histidine-rich glycoprotein**
AUTHOR(S): Silverstein, Roy L.; Leung, Lawrence L. K.; Harpel, Peter C.; Nachman, Ralph L.
CORPORATE SOURCE: Cornell Med. Cent., New York Hosp., New York, NY, 10021, USA
SOURCE: J. Clin. Invest. (1985), 75(6), 2065-73
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purified human platelet **thrombospondin** (TSP) formed a trimol. complex with human plasminogen (Plg) and **histidine -rich glycoprotein** (**HRGP**). Complex formation was detected by a specific ELISA which demonstrated simultaneous binding of fluid-phase Plg and **HRGP** to TSP adsorbed to microtitration wells. Neither ligand inhibited complex formation of the other with TSP, but 10 mM .epsilon.-amino-n-caproic acid selectively blocked incorporation of Plg into the complex, suggesting that TSP contains independent binding sites for Plg and **HRGP**. A comparable extent of trimol. complex formation was also detected when TSP monomer was substituted for whole TSP in the ELISA. **HRGP** covalently crosslinked to Sepharose 4B simultaneously bound both [125I]TSP and [131I]Plg, confirming trimol. complex formation. Rocket immunoelectrophoresis of mixts. of the purified radiolabeled proteins into anti-Plg contg. agarose also confirmed trimol. complex formation. The TSP-**HRGP** -Plg complex bound a similar amt. of heparin as the TSP-**HRGP** complex, demonstrating that the **HRGP** within the trimol. complex maintained functional capability. Similarly, using a fluorometric plasmin substrate, the trimol. complex was shown to be an effective substrate for tissue plasminogen activator. Significant amts. of plasmin were generated from the TSP-**HRGP**-Plg complex (equiv. to that from the TSP-Plg complex), but the rate of plasmin generation from the trimol. complex was greater than from the bimol. complex, suggesting an important interaction of **HRGP** with Plg when both are complexed to TSP. The macromol. assembly of these 3 proteins on cellular surfaces, e.g., on platelets, may serve important regulatory functions, both prothrombotic at sites of active fibrin deposition and proteolytic in nonfibrin-contg. microenvironments.

L4 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1984:81489 CAPLUS
DOCUMENT NUMBER: 100:81489
TITLE: Complex formation of platelet **thrombospondin** with **histidine-rich glycoprotein**
AUTHOR(S): Leung, Lawrence L. K.; Nachman, Ralph L.; Harpel, Peter C.
CORPORATE SOURCE: Cornell Med. Cent., New York Hosp., NY, 10021, USA
SOURCE: J. Clin. Invest. (1984), 73(1), 5-12
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Thrombospondin** and **histidine-rich glycoprotein** are 2 proteins with diverse biol. activities which have been assocd. with human platelets and other cell systems. By using an enzyme-linked immunosorbent assay, it was demonstrated that purified human platelet **thrombospondin** formed a complex with purified human plasma **histidine-rich glycoprotein**. The formation of the **thrombospondin -histidine-rich glycoprotein** complex was specific, concn. dependent, and saturable. Significant binding was detected when **histidine-rich glycoprotein** was incubated with **thrombospondin** immobilized on anti-**thrombospondin** IgG-coated plates, indicating that the obsd. complex formation was not due to a **thrombospondin** interaction with the plastic surface. Sucrose d.-gradient ultracentrifugation of a mixt. of **thrombospondin** and **histidine-rich glycoprotein** also revealed the formation of fluid-phase complexes, with an estd. stoichiometry of 1 **thrombospondin** : 3.5 **histidine-rich glycoproteins**. Fibrinogen, previously shown to bind to adsorbed **thrombospondin**, did not inhibit the formation of the **thrombospondin-histidine-rich glycoprotein** complex. **Histidine-rich glycoprotein** complexed with **thrombospondin** was capable of binding heparin and neutralizing the anticoagulant activity of heparin in plasma. Specific complex formation between **thrombospondin** and **histidine-rich glycoprotein** may play a significant role in influencing platelet blood vessel wall interactions as well as in modulating the assocn. of various cells with the extracellular matrix.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, INCST LPLUS, JAPIO' ENTERED AT 09:58:23 ON 21 JUN 2001)
L5 67 S L4
L6 32 DUP REM L5 (35 DUPLICATES REMOVED)

Searcher : Shears 308-4994

L6 ANSWER 1 OF 32 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2001:421418 SCISEARCH
THE GENUINE ARTICLE: 424WZ
TITLE: **Histidine-rich glycoprotein (HRGP)** modulates the antiangiogenic activity of **thrombospondin** -1 (TSP-1).
AUTHOR: Simantov R (Reprint); Febbraio M; Nachman R L; Silverstein R L
CORPORATE SOURCE: Cornell Univ, Weill Med Coll, New York, NY USA
COUNTRY OF AUTHOR: USA
SOURCE: ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY, (APR 2001) Vol. 21, No. 4, pp. 706-706. MA 271. Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 1079-5642.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L6 ANSWER 2 OF 32 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001321553 MEDLINE
DOCUMENT NUMBER: 21072588 PubMed ID: 11204593
TITLE: Genetic screening of candidate genes for a prothrombotic interaction with type I protein C deficiency in a large kindred.
AUTHOR: Scott B T; Bovill E G; Callas P W; Hasstedt S J; Leppert M F; Valliere J E; Varvil T S; Long G L
CORPORATE SOURCE: Department of Pathology, University of Vermont, Burlington 05405, USA.
CONTRACT NUMBER: P01 HL46703 (NHLBI)
RR00109 (NCRR)
SOURCE: THROMBOSIS AND HAEMOSTASIS, (2001 Jan) 85 (1) 82-7. Journal code: VQ7; 7608063. ISSN: 0340-6245.
PUB. COUNTRY: Germany: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010611
Last Updated on STN: 20010611
Entered PubMed: 20010201
Entered Medline: 20010607
AB The incomplete penetrance of thrombosis in familial protein C deficiency suggests disease occurs when this deficit is combined with additional abnormalities in the hemostatic system. The pattern of inherited thrombophilia in the Vermont II kindred, which is

affected by a clinically dominant type I protein C deficiency, provides strong evidence for a second unidentified gene that segregates independently of protein C deficiency and increases susceptibility to thrombosis. To test the second gene hypothesis, thirty-four candidate genes for proteins involved in hemostasis or inflammation were tested as the unknown defect, using highly polymorphic short tandem repeat (STR) markers in an informative subset (n = 31) of the kindred. The genes considered are; alpha-fibrinogen, beta-fibrinogen, gamma-fibrinogen, prothrombin, tissue factor, factor V, protein S, complement component 4 binding protein, factor XI, factor XII, factor XIIIa, factor XIIIb, **histidine rich glycoprotein**, high molecular weight kininogen, kallikrein, von Willebrands factor, platelet factor 4, **thrombospondin**, antithrombin III, alpha-1-antitrypsin, thrombomodulin, plasminogen, tissue plasminogen activator, urokinase plasminogen activator, plasminogen activator inhibitor-1, plasminogen activator inhibitor-2, protein C inhibitor, alpha-2-plasmin inhibitor, kallistatin, lipoprotein a, interleukin 6, interleukin 1, cystathionine-beta-synthase, and methylenetetrahydrofolate reductase. Mutations in many of these genes have been previously established as independent risk factors for thrombosis. However, linkage analysis provided no evidence to implicate any of the candidate genes as the second inherited factor that promotes thrombophilia in this kindred.

L6 ANSWER 3 OF 32 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 2001111447 MEDLINE
DOCUMENT NUMBER: 20576573 PubMed ID: 11134179
TITLE: **Histidine-rich glycoprotein** inhibits the antiangiogenic effect of **thrombospondin**-1.
AUTHOR: Simantov R; Febbraio M; Crombie R; Asch A S; Nachman R L; Silverstein R L
CORPORATE SOURCE: Division of Hematology-Oncology, Department of Medicine, Weill Medical College of Cornell University, New York, New York 10021, USA.. rsimant@mail.med.cornell.edu
CONTRACT NUMBER: M01 RR-00047 (NCRR)
R01 HL-42540 (NHLBI)
R29 HL-58559 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (2001 Jan) 107 (1) 45-52.
Journal code: HS7. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200102

ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010202

AB Angiogenesis is critical for the growth and proliferation of tumors as well as for normal development. We now describe a novel role for **histidine-rich glycoprotein** (**HRGP**) in the modulation of angiogenesis. **HRGP** is a plasma protein that circulates in relatively high concentrations (1.5 microM), but has no known function in vivo. We have shown previously that **HRGP** binds with high affinity to **thrombospondin**-1 (TSP-1), a homotrimeric glycoprotein that is a potent inhibitor of angiogenesis. The antiangiogenic activity of TSP-1 is mediated by the binding of properdin-like type I repeats to the receptor CD36. We found that binding of **HRGP** to TSP-1 was similarly mediated by TSP type I repeats. **HRGP** colocalized with TSP-1 in the stroma of human breast cancer specimens, and this interaction masked the antiangiogenic epitope of TSP-1. In assays performed in vitro of endothelial cell migration and tube formation, and in vivo corneal angiogenesis assays, **HRGP** inhibited the antiangiogenic effect of TSP-1. These studies suggest that **HRGP** can modulate the antiangiogenic activity of TSP-1, and identify a potential mechanism of resistance to the antiangiogenic effect of TSP-1.

L6 ANSWER 4 OF 32 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001132962 MEDLINE
DOCUMENT NUMBER: 21060443 PubMed ID: 10749676
TITLE: **Thrombospondin**-1 binds to polyhistidine with high affinity and specificity.
AUTHOR: Vanguri V K; Wang S; Godyna S; Ranganathan S; Liau G
CORPORATE SOURCE: Department of Vascular Biology, Jerome H. Holland Laboratory, American Red Cross, Rockville, MD 20855, USA.
CONTRACT NUMBER: HL37510 (NHLBI)
HL56063 (NHLBI)
SOURCE: BIOCHEMICAL JOURNAL, (2000 Apr 15) 347 (Pt 2) 469-73.
Journal code: 9YO; 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered PubMed: 20010126
Entered Medline: 20010301

AB **Thrombospondin**-1 (TSP1) is a secreted trimeric glycoprotein of 450 kDa with demonstrated effects on cell growth,

adhesion and migration. Its complex biological activity is attributed to its ability to bind to cell-surface receptors, growth factors and extracellular-matrix proteins. In this study, we used a (125)I solid-phase binding assay to demonstrate that TSP1 binds specifically to proteins containing polyhistidine stretches. Based on studies with three different six-histidine-containing recombinant proteins, we derived an average dissociation constant of 5 nM. The binding of (125)I-labelled TSP1 to these proteins was inhibited by peptides containing histidine residues, with the degree of competition being a function of the number of histidines within the peptide. Binding was not inhibited by excess histidine or imidazole, indicating that the imidazole ring is not sufficient for recognition by TSP1. Heparin was a potent inhibitor of binding with a K(i) of 50 nM, suggesting that the heparin-binding domain of TSP1 may be involved in this interaction. This was confirmed by the ability of a recombinant heparin-binding domain of TSP1 to directly compete for TSP1 binding to polyhistidine-containing proteins. Affinity chromatography with a polyhistidine-containing peptide immobilized on agarose revealed that TSP1 in platelet releasates is the major polypeptide retained on the six-histidine-peptide column. We conclude that TSP1 contains a high-affinity binding site for polyhistidine and this is likely to be the molecular basis for the observed binding of TSP1 to **histidine-rich glycoprotein**. The possibility that other polyhistidine-containing proteins also interact with TSP1 warrants further study.

L6 ANSWER 5 OF 32 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 4
ACCESSION NUMBER: 2001:300247 BIOSIS
DOCUMENT NUMBER: PREV200100300247
TITLE: **Histidine rich glycoprotein** (**HRGP**) inhibits the angiostatic activity of **thrombospondin**-1 (TSP-1) in vivo.
AUTHOR(S): Simantov, Ronit (1); Febbraio, Maria (1); Nachman, Ralph L. (1); Crombie, Rene (1); Silverstein, Roy L. (1)
CORPORATE SOURCE: (1) Division of Hematology-Oncology, Department of Medicine, Weill Medical College of Cornell University, New York, NY USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 34a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology . ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

SUMMARY LANGUAGE: English

AB Angiogenesis is critical for normal development and for tumor growth. We now describe a novel role for **histidine-rich glycoprotein** (**HRGP**), a 66 kDa platelet and plasma protein, in the modulation of angiogenesis. We have previously shown that **HRGP** binds with high affinity to **thrombospondin**-1 (TSP-1), a potent inhibitor of angiogenesis. The angiostatic activity of TSP-1 is mediated by the binding of its properidin-like type I repeats to the receptor CD36. We have shown that binding of **HRGP** to TSP-1 was similarly mediated by the type I repeats, and that **HRGP** abrogated the inhibitory effect of TSP-1 on endothelial cell migration and tube formation in vitro. To explore whether **HRGP** blocks the angiostatic activity of TSP-1 in vivo, we implanted Hydron pellets containing bFGF, TSP-1, and/or **HRGP** in the corneas of C57B1/6 mice. After 6 days, vigorous outgrowth of blood vessels was seen in 13/13 eyes implanted with pellets containing bFGF (50ng) and in only 2/11 eyes implanted with pellets containing both bFGF and TSP-1 (200ng). In mice implanted with pellets containing bFGF, TSP-1, and **HRGP** (100 ng, **HRGP**:TSP-1 molar ratio =3:1), angiogenesis was seen in 10/10 eyes ($p=0.02$, chi square analysis), suggesting that **HRGP** blocked the angiostatic effect of TSP-1. Pellets containing **HRGP** alone did not induce angiogenesis. In CD36-null mice, TSP-1 did not inhibit bFGF-induced angiogenesis, nor did **HRGP** induce angiogenesis in the absence of bFGF. To explore further the in vivo interactions of **HRGP** with TSP-1, we performed immunohistochemical studies on sections of human breast cancer specimens. We found that **HRGP** co-localized with TSP-1 in stromal connective tissue, while in adjacent epithelium only TSP-1 was detected. To study the role of the type 1 repeat in TSP-1-**HRGP** interactions in tumor stroma, we developed a specific antibody to a type I repeat peptide (CSVTCG). We found that the CSVCTG epitope was detectable in the epithelium where TSP-1 was present and **HRGP** was absent, but in the stroma where **HRGP** co-localized with TSP-1, there was no detectable CSVCTG reactivity. These data suggest that the association of TSP-1 with **HRGP** in vivo masks the antiangiogenic type I epitope of TSP-1. **HRGP** may serve to regulate the angiogenic "switch" by interfering with TSP-1-CD36 interactions, thereby promoting angiogenesis and tumor growth.

L6 ANSWER 6 OF 32 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-013232 [01] WPIDS
DOC. NO. NON-CPI: N2000-010261
DOC. NO. CPI: C2000-002503
TITLE: Novel polypeptide bioactive factors, designated matrix binding factors, used for treatment of

pathological conditions, in tissue culture, and for preparation of surgical implants or prostheses.

DERWENT CLASS: B04 C06 D16 D21 D22 P34
INVENTOR(S): BALLARD, F J; HUMPHRYS, S T
PATENT ASSIGNEE(S): (BELF-I) BELFORD D A; (GROP-N) GROPEP PTY LTD; (GROP-N) GROPEP LTD
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9954359	A1	19991028	(200001)*	EN	70
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP US					
AU 9933989	A	19991108	(200014)		
EP 1071718	A1	20010131	(200108)	EN	
R: DE FR GB IT					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9954359	A1	WO 1999-AU292	19990419
AU 9933989	A	AU 1999-33989	19990419
EP 1071718	A1	EP 1999-915364	19990419
		WO 1999-AU292	19990419

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9933989	A	Based on	WO 9954359
EP 1071718	A1	Based on	WO 9954359

PRIORITY APPLN. INFO: AU 1998-2984 19980417
AN 2000-013232 [01] WPIDS
AB WO 9954359 A UPAB: 20000105
NOVELTY - A recombinant MBF (I), comprising a polypeptide bioactive factor in which the naturally occurring amino acid sequence has been modified to introduce one or more amino acid substitutions, deletions and/or additions which increased the affinity of the factor for a negatively-charged site of surface, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid (II) encoding (I), which especially a sense cDNA;

(2) an expression vector comprising (II);

(3) a composition comprising (I), with a pharmaceutically or

vetinarily acceptable carrier;

(4) a composition for the enhancement of tissue remodeling or tissue repair associated with trauma or healing, comprising (I), formulated with a carrier suitable for topical application;

(5) a composition for alleviation of skin damage associated with aging or exposure to UV or radiation, comprising (I) with a cosmetically acceptable carrier;

(6) a composition for the treatment or prevention of a condition associated with an impaired gut function, comprising (I) formulated with a carrier suitable to produce an orally stable, bioactive enteral formulation;

(7) a composition for the targeting and localisation of (I) to cells or tissue, thereby promoting cell adhesion, growth, migration or activity, comprising (I) formulated in a sterile injectible carrier;

(8) a cell or tissue culture supplement, comprising (I);

(9) a tissue culture vessel or insert, comprising a negatively-charged surface pre-treated with (I);

(10) a surgical prosthesis, comprising a negatively-charged surface pre-treated with (I);

(11) a method of producing a recombinant (I), comprising subcloning (II) into a cloning vector, and subjecting the vector to mutagenesis to generate (I);

(12) a method for promoting adhesion, growth, migration or activity of cells on a negatively-charged surface, comprising growing the cells (especially vertebrate or insect cells) in a culture medium in the presence of (I);

(13) a method for the prevention of periodontal disease, comprising administering (I); and

(14) a method of cosmetic delivery, comprising administering (I) to the skin or hair of an animal.

ACTIVITY - Wound healing; vulnery; antiinflammatory.

MECHANISM OF ACTION - None given.

USE - The matrix binding factors (MBFs) of the invention have a wide variety of uses, including:

(i) maintenance, growth or differentiation of animal cell in culture, and of one or more organized cellular structures (claimed), e.g. skin, cartilage, tendon, ligament or bone;

(ii) coating a negatively-charged surface to promote cell adhesion, growth, migration or activity (claimed), e.g. culture vessels for use in keratinocyte expansion to provide partial thickness skin grafts for burns patients or for coating of a surgical implant or prosthesis;

(iii) enhancement of tissue remodeling and repair associated with trauma or manipulation (claimed), e.g. treatment of wounds or burns;

(iv) as an orally active product for the prevention and/or treatment of impaired gut function or periodontal disease (claimed);

(v) facilitating tissue targeting following systemic administration, e.g. localization of the factor to bone matrix following intravenous injection; and

(vi) maintaining higher bioactive factor concentrations at the site of administration in order to effect a prolonged pharmacological action.

The factors may also be used in conjunction with other growth factors or therapeutic agents, and used in compositions to promote adhesion, growth or migration, to prevent apoptosis, and to alleviate skin damage associated with aging or exposure to radiation or UV (all claimed).

ADVANTAGE - None given.

Dwg.0/3

L6 ANSWER 7 OF 32 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2000:53878 SCISEARCH
THE GENUINE ARTICLE: 257PH
TITLE: **Histidine rich glycoprotein** (**HRGP**) inhibits the antiangiogenic effect of **thrombospondin**-I (TSP-1).
AUTHOR: Simantov R (Reprint); Nachman R L; Febbraio M; Asch A S; Silverstein R L
CORPORATE SOURCE: CORNELL UNIV, WEILL MED COLL, DEPT MED, DIV HEMATOL ONCOL, NEW YORK, NY
COUNTRY OF AUTHOR: USA
SOURCE: BLOOD, (15 NOV 1999) Vol. 94, No. 10, Part 1, Supp. [1], pp. 2753-2753.
Publisher: AMER SOC HEMATOLOGY, 1200 19TH ST, NW, STE 300, WASHINGTON, DC 20036-2422.
ISSN: 0006-4971.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L6 ANSWER 8 OF 32 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:46772 BIOSIS
DOCUMENT NUMBER: PREV200000046772
TITLE: **Histidine rich glycoprotein** (**HRGP**) inhibits the anti-angiogenic effect of **thrombospondin**-I (TSP-1.
AUTHOR(S): Simantov, R. (1); Nachman, R. L. (1); Febbraio, M. (1); Asch, A. S. (1); Silverstein, R. L. (1)
CORPORATE SOURCE: (1) Division of Hematology/Oncology, Department of Medicine, Weill Medical College of Cornell University, New York, NY USA

SOURCE: Blood, (Nov. 15, 1999) Vol. 94, No. 10 SUPPL. 1 PART 1, pp. 619a.
Meeting Info.: Forty-first Annual Meeting of the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999 The American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L6 ANSWER 9 OF 32 MEDLINE DUPLICATE 5

ACCESSION NUMBER: 1999085040 MEDLINE
DOCUMENT NUMBER: 99085040 PubMed ID: 9867861
TITLE: Interaction of recombinant procollagen and properdin modules of **thrombospondin**-1 with heparin and fibrinogen/fibrin.
AUTHOR: Panetti T S; Kudryk B J; Mosher D F
CORPORATE SOURCE: Departments of Medicine and Biomolecular Chemistry, University of Wisconsin, Madison, Wisconsin 53706, USA.. tpanetti@facstaff.wisc.edu
CONTRACT NUMBER: HL09150 (NHLBI)
HL54462 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jan 1) 274 (1) 430-7.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990205

AB Many properties have been assigned to the procollagen and properdin (Type I) modules of **thrombospondin**-1 (TSP1) based on activities of large proteolytic fragments of TSP1 or peptides containing TSP1-derived sequences. To examine the activities of the modules more exactly, we expressed the first properdin module (P1); the third properdin module (P3); the first and second properdin modules (P12); the first, second, and third properdin modules (P123); and the procollagen module with the first, second, and third properdin modules (CP123) in the GELEX expression vector (GE1) using the baculovirus system. GE1 encodes the pre-pro sequence, the transglutaminase cross-linking site(s), the protease-sensitive site, and the gelatin binding domain from the amino terminus of rat fibronectin. All five recombinant proteins were expressed by insect cells, secreted into the culture medium, and purified by gelatin-agarose affinity chromatography. P123 shared with TSP1 a

resistance to trypsin unless reduced and alkylated. P12/GE1, P123/GE1, and CP123/GE1 bound poorly to heparin-agarose except in the absence of sodium chloride, whereas peptides based on P2 are known to bind to heparin in up to 150 mM sodium chloride. In cross-linking experiments employing activated recombinant factor XIII and the transglutaminase cross-linking site in the fibronectin-derived sequence, P12/GE1, P123/GE1, CP123/GE1, and P3/GE1 but not P1/GE1 became incorporated into a fibrin clot more than GE1 alone. Analysis of the complex indicated that cross-linking was to the portion of the fibrin alpha-chain remaining in the D-dimer of plasmin digests. P123 also cross-linked to the Aalpha-chain of unclotted fibrinogen. P123 competed for 125I-TSP1 incorporation into the fibrin clot. P123 did not cross-link to plasminogen, **histidine-rich glycoprotein**, fibronectin, or plasma globulins other than fibrinogen/fibrin. These results indicate that the properdin modules of TSP1 specifically interact with fibrinogen/fibrin but not with heparin under physiologic conditions.

L6 ANSWER 10 OF 32 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:96694 BIOSIS
DOCUMENT NUMBER: PREV199799395897
TITLE: Expression and characterization of the properdin modules of **thrombospondin**-1.
AUTHOR(S): Panetti, T. S.; Getzler, S. B.; Mosher, D. F.
CORPORATE SOURCE: Univ. Wisconsin, Madison, WI 53706 USA
SOURCE: Molecular Biology of the Cell, (1996) Vol. 7, No. SUPPL., pp. 411A.
Meeting Info.: Annual Meeting of the 6th International Congress on Cell Biology and the 36th American Society for Cell Biology San Francisco, California, USA December 7-11, 1996
ISSN: 1059-1524.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L6 ANSWER 11 OF 32 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 96:804069 SCISEARCH
THE GENUINE ARTICLE: VP829
TITLE: BLOOD-TYPE AND AGE AFFECT HUMAN PLASMA-LEVELS OF **HISTIDINE-RICH GLYCOPROTEIN** IN A LARGE POPULATION
AUTHOR: DRASIN T; SAHUD M (Reprint)
CORPORATE SOURCE: COAGULAT CTR, SHERRICK RES BLDG, 3023 SUMMIT ST, OAKLAND, CA, 94609 (Reprint); COAGULAT CTR, OAKLAND, CA, 94609
COUNTRY OF AUTHOR: USA
SOURCE: THROMBOSIS RESEARCH, (01 NOV 1996) Vol. 84, No. 3,

pp. 179-188.
ISSN: 0049-3848.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 24

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Histidine-rich glycoprotein** (HRG) is an alpha(2)-glycoprotein that was first described by Heimberger, et al, in 1972. Today, HRG is generally regarded as a mild prothrombotic protein. Blood samples of 585 individuals were collected with the aid of the Alameda-Contra Costa Medical Association (ACCMA) Blood Bank, Oakland, CA. Sex, age, ethnic origin, and blood-type information were available for each sample. The blood was processed to isolate the cell free plasma, and plasma HRG concentration was measured relative to that of a normal pool through a modified Laurell technique. Among Caucasian individuals, the mean HRG level of blood-type AB subjects, 125+/-28%, was found to be significantly greater than the means for subjects with A and O blood-types, 103+/-35% and 105+/-30% respectively (P=.0246). In addition, the average HRG level appears to increase linearly with age. The mean plasma-level of HRG in subjects 50-59 years old was significantly greater than the level in subjects 30-39 years old (P=.0020). The correlation observed between blood-type and plasma HRG level in this study supports previously reported results that indicate significant genetic control over the plasma level of this protein. The age and blood-type based correlations observed in this study raise the question of whether these variables need be addressed if HRG level were to be employed in a clinical setting as a diagnostic tool. Copyright (C) 1996 Elsevier Science Ltd

L6 ANSWER 12 OF 32 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1994:121916 BIOSIS
DOCUMENT NUMBER: PREV199497134916
TITLE: Prevalence of elevated **histidine-rich glycoprotein** in patients with thrombophilia: A study of 695 patients.
AUTHOR(S): Ehrenforth, S. (1); Aygoeren-Puersuen, E.; Hach-Wunderle, V.; Scharrer, I.
CORPORATE SOURCE: (1) Centre Internal Med., Dep. Angiol., HS 13a, J.W. Goethe Univ. Hosp., Theodor-Stern-Kai 7, 60596 Frankfurt Am Main Germany
SOURCE: Thrombosis and Haemostasis, (1994) Vol. 71, No. 1, pp. 160-161.
ISSN: 0340-6245.
DOCUMENT TYPE: Letter
LANGUAGE: English

L6 ANSWER 13 OF 32 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 94:44788 SCISEARCH
THE GENUINE ARTICLE: MQ902
TITLE: PREVALENCE OF ELEVATED **HISTIDINE-RICH GLYCOPROTEIN** IN PATIENTS WITH THROMBOPHILIA - A STUDY OF 695 PATIENTS
AUTHOR: EHRENFORTH S (Reprint); AYGORENPURSUN E; HACHWUNDERLE V; SCHARRER I
CORPORATE SOURCE: JW GOETHE UNIV HOSP, CTR INTERNAL MED, DEPT ANGIOL, HS13A, THEODOR STERN KAI 7, D-60596 FRANKFURT, GERMANY (Reprint)
COUNTRY OF AUTHOR: GERMANY
SOURCE: THROMBOSIS AND HAEMOSTASIS, (JAN 1994) Vol. 71, No. 1, pp. 160-161.
ISSN: 0340-6245.
DOCUMENT TYPE: Letter; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 20

L6 ANSWER 14 OF 32 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 94218873 MEDLINE
DOCUMENT NUMBER: 94218873 PubMed ID: 8165617
TITLE: Interaction of immobilised unfractionated and LMW heparins with proteins in whole human plasma.
AUTHOR: Zammit A; Pepper D S; Dawes J
CORPORATE SOURCE: Heart Research Institute, Sydney, Australia.
SOURCE: THROMBOSIS AND HAEMOSTASIS, (1993 Dec 20) 70 (6) 951-8.
Journal code: VQ7; 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199405
ENTRY DATE: Entered STN: 19940606
Last Updated on STN: 19940606
Entered Medline: 19940523

AB The profile of proteins bound to immobilised heparins in hirudin-anticoagulated human plasma was analysed. In molar terms, antithrombin III was the most abundant protein bound to therapeutic doses of unfractionated heparin (M(r) = 12,000), whereas heparin cofactor II constituted < 1% of the protein bound. **Histidine-rich glycoprotein** was the only plasma protein likely to influence anticoagulant activity by direct competition with antithrombin III, though significant quantities of complement Factor H, fibrinogen, fibronectin, vitronectin and apolipoprotein B were also detected. Only traces of von Willebrand factor, complement

factor I, inter-alpha-trypsin inhibitor, alpha 2-macroglobulin, serum amyloid P and transferrin were identified, and neither **thrombospondin** nor platelet factor 4 were measurable. Binding of both antithrombin III and **histidine-rich glycoprotein** varied with the ratio of heparin to plasma. Clexane (M(r) = 4,500) also bound antithrombin III, but both **histidine-rich glycoprotein** and vitronectin were quantitatively significant neutralising proteins. Neutralising proteins dominated the binding profile for Oligo H (M(r) = 2,200).

L6 ANSWER 15 OF 32 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93148700 EMBASE
DOCUMENT NUMBER: 1993148700
TITLE: **Histidine-rich glycoprotein**: An abundant plasma protein in search of a function.
AUTHOR: Leung L.
CORPORATE SOURCE: Gilead Sciences, 346 Lakeside Drive,Foster City, CA 94404, United States
SOURCE: Journal of Laboratory and Clinical Medicine, (1993) 121/5 (630-631).
ISSN: 0022-2143 CODEN: JLCMAK
COUNTRY: United States
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English

L6 ANSWER 16 OF 32 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 93:494193 SCISEARCH
THE GENUINE ARTICLE: LR041
TITLE: THE FUNCTIONS OF **THROMBOSPONDIN** AND ITS INVOLVEMENT IN PHYSIOLOGY AND PATHOPHYSIOLOGY
AUTHOR: LAHAV J (Reprint)
CORPORATE SOURCE: BEILINSON MED CTR, INST HEMATOL, IL-49100 PETAH TIQWA, ISRAEL (Reprint); TEL AVIV UNIV, SACKLER FAC MED, IL-69978 TEL AVIV, ISRAEL
COUNTRY OF AUTHOR: ISRAEL
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (04 AUG 1993) Vol. 1182, No. 1, pp. 1-14.
ISSN: 0006-3002.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 163

L6 ANSWER 17 OF 32 SCISEARCH COPYRIGHT 2001 ISI (R)

ACCESSION NUMBER: 92:112996 SCISEARCH
THE GENUINE ARTICLE: HD434
TITLE: **THROMBOSPONDIN**-II - PARTIAL CDNA SEQUENCE, CHROMOSOME LOCATION, AND EXPRESSION OF A 2ND MEMBER OF THE **THROMBOSPONDIN** GENE FAMILY IN HUMANS
AUTHOR: LABELL T L (Reprint); MILEWICZ D J M; DISTECHE C M; BYERS P H
CORPORATE SOURCE: UNIV WASHINGTON, DEPT PATHOL, SEATTLE, WA, 98195 (Reprint); UNIV WASHINGTON, CTR INHERITED DIS, SEATTLE, WA, 98195; UNIV WASHINGTON, DEPT MED, SEATTLE, WA, 98195
COUNTRY OF AUTHOR: USA
SOURCE: GENOMICS, (MAR 1992) Vol. 12, No. 3, pp. 421-429. ISSN: 0888-7543.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 67

L6 ANSWER 18 OF 32 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 89255263 MEDLINE
DOCUMENT NUMBER: 89255263 PubMed ID: 2566603
TITLE: Interaction of **histidine-rich glycoprotein** with human T lymphocytes.
AUTHOR: Saigo K; Shatsky M; Levitt L J; Leung L K
CORPORATE SOURCE: Department of Medicine, Stanford University Medical School, California 94305.
CONTRACT NUMBER: 1RO1-HL35774 (NHLBI)
2K08-HL01790-07 (NHLBI)
K04 HL 02213-01 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1989 May 15) 264 (14) 8249-53.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198906
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19970203
Entered Medline: 19890630

AB **Histidine-rich glycoprotein** (**HRGP**), a human plasma and platelet protein, interacts with multiple ligands in vitro, including heparin, plasminogen, **thrombospondin**, and fibrinogen/fibrin. In this study, the binding of **HRGP** to human T lymphocytes was characterized. The binding was specific, concentration-dependent, saturable, and

reversible. Scatchard plot analysis revealed two classes of binding sites: the high affinity class had an apparent dissociation constant (Kd) of 1.92 X 10(-8) M, with 0.92 X 10(4) sites/cell, and the low affinity class had a Kd of 4.97 X 10(-7) M, with 3.7 X 10(4) sites/cell. **HRGP** binding to T cells in the presence of **HRGP**-depleted serum was comparable to that observed in buffer. Dot-blot analysis showed that **HRGP** bound to specific T cell proteins. Using both **HRGP** affinity chromatography and immunoprecipitation with affinity-purified anti-**HRGP** IgG, a major 56-kDa **HRGP**-binding protein in surface labeled T cell lysates was demonstrated. The 56-kDa protein was shown not to be related to the CD2 molecule on T cells. The binding characteristics of **HRGP** to T lymphocytes indicate a specific ligand-receptor interaction. This is the first demonstration of **HRGP** binding to a cell surface, and its binding to human T cells may play an important role in T lymphocyte biology.

L6 ANSWER 19 OF 32 JICST-EPlus COPYRIGHT 2001 JST
ACCESSION NUMBER: 880520647 JICST-EPlus
TITLE: Proteases in thrombus formation and its regulation.
AUTHOR: SUZUKI KOJI
CORPORATE SOURCE: Mie Univ., Faculty of Medicine
SOURCE: Saishin Igaku, (1988) vol. 43, no. 4, pp. 757-764.
Journal Code: Z0358A (Fig. 3, Tbl. 2, Ref. 10)
CODEN: SAIGAK; ISSN: 0370-8241
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Commentary
LANGUAGE: Japanese
STATUS: New

AB Thrombus formation depends on the states of vessel wall, platelet, blood coagulation and fibrinolysis. In particular, blood coagulation and its regulation systems deeply participate in it. Many serine protease zymogens(Factor XII, Factor XI, plasma prekallikrein, Factor IX, Factor X, Factor VII, prothrombin, protein C, plasminogen activators(t-PA and prourokinase), plasminogen), cofactor proteins(high molecular weight kininogen, Factor V, Factor VIII, tissue factor, protein S, thrombomodulin), protease inhibitors(antithrombin III, heparin cofactor II, .ALPHA.1 antitrypsin, C1 inactivator, .ALPHA.2 macroglobulin, protein C inhibitor, t-PA inhibitor, .ALPHA.2 plasmin inhibitor) and modulator proteins(**thrombospondin**, **histidine-rich glycoprotein**) are involved in the thrombus formation and its regulation. Expression of functions of these proteins strongly depends upon pathophysiological states of vascular wall and blood cells. Quantitative balance of procoagulant and anticoagulant proteins is also important for control of thrombus formation. Disorder of this balance, e.g., increase of procoagulant

proteins(t-PA inhibitor, **histidine-rich glycoprotein**, etc.) and decrease of anticoagulant proteins(antithrombin III, heparin cofactor II, protein C, protein S, etc.), has been known to induce thrombotic disease frequently.(author abst.)

L6 ANSWER 20 OF 32 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 88070666 MEDLINE
DOCUMENT NUMBER: 88070666 PubMed ID: 3686023
TITLE: Binding of **thrombospondin** to immobilized ligands: specific interaction with fibrinogen, plasminogen, **histidine-rich glycoprotein**, and fibronectin.
AUTHOR: Walz D A; Bacon-Baguley T; Kendra-Franczak S; DePoli P
CORPORATE SOURCE: Wayne State University, Department of Physiology, Detroit, Michigan 48201.
CONTRACT NUMBER: HL 27073 (NHLBI)
T32 HL 07602 (NHLBI)
SOURCE: SEMINARS IN THROMBOSIS AND HEMOSTASIS, (1987 Jul) 13 (3) 317-25.
Journal code: UKS; 0431155. ISSN: 0094-6176.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198801
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19980206
Entered Medline: 19880104

L6 ANSWER 21 OF 32 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 86278037 MEDLINE
DOCUMENT NUMBER: 86278037 PubMed ID: 2942536
TITLE: Tissue plasminogen activator and urokinase enhance the binding of plasminogen to **thrombospondin** .
AUTHOR: Silverstein R L; Harpel P C; Nachman R L
CONTRACT NUMBER: HL18828 (NHLBI)
HL30649 (NHLBI)
K11HLAM1442 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1986 Jul 25) 261 (21) 9959-65.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 198609
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 20000303
Entered Medline: 19860917

AB **Thrombospondin** (TSP) is a multifunctional platelet alpha-granule and extracellular matrix glycoprotein that binds specifically to plasminogen (Plg) via that protein's lysine-binding site and modulates activation by tissue activator (TPA). In this study we report that the plasminogen activators, TPA and urokinase, greatly influence the binding of Plg to TSP. Using an enzyme-linked immunosorbent assay and a TSP-Sepharose affinity bead-binding assay we have found that Plg-TSP complex formation was markedly enhanced (up to 5-fold) when catalytic concentrations of Plg activators were included in the reaction mixtures. The enhancement was dependent upon the generation of small amounts of active plasmin and was duplicated by pretreatment of the immobilized TSP with plasmin prior to addition of the Plg. The enhancement effect was associated with selective proteolysis of the immobilized TSP. Purified Lys-Plg (the plasmin modified form of native Glu-Plg) bound to TSP to a greater extent than Glu-Plg, and binding of both forms was augmented by Plg activators. The apparent KD values of complex formation were unchanged in the presence of Plg activators suggesting that the enhancement effect was due to the generation of additional binding sites. The increased amount of bound Plg was demonstrated to result in a similar increase in the amount of plasmin generated from the complexes by TPA. Plg activators did not influence binding of Plg to **histidine-rich glycoprotein** or of **histidine-rich glycoprotein** to TSP, demonstrating specificity. In addition when TSP was treated with other proteases (human thrombin or human leukocyte elastase) no augmentation of Plg binding was seen. Thus, the initial production of small amounts of plasmin from Plg immobilized on TSP in fibrin-free microenvironments could generate a positive feedback loop by enzymatically modifying both TSP and Plg, resulting in an increase in TSP-Plg complex formation leading to the localized production of substantially more plasmin.

L6 ANSWER 22 OF 32 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 86206062 MEDLINE
DOCUMENT NUMBER: 86206062 PubMed ID: 2939460
TITLE: Human brain glial cells synthesize **thrombospondin**.
AUTHOR: Asch A S; Leung L L; Shapiro J; Nachman R L
CONTRACT NUMBER: 1KO8 HL01567-01 (NHLBI)
HL18828 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1986 May) 83 (9) 2904-8.

Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198606
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19980206
Entered Medline: 19860606

AB **Thrombospondin**, a 450-kDa multinodular glycoprotein with lectin-type activity, is found in human platelets, endothelial cells, fibroblasts, smooth muscle cells, monocytes, and granular pneumocytes. **Thrombospondin** interacts with heparin, fibrinogen, fibronectin, collagen, **histidine-rich glycoprotein**, and plasminogen. Recently, **thrombospondin** synthesis by smooth muscle cells has been reported to be augmented by platelet-derived growth factor. We present evidence that **thrombospondin** is present within and synthesized by astrocytic neuroglial cells. Heparin-Sepharose affinity chromatography of material derived from a human brain homogenate yielded a protein that, when reduced, had an apparent size of 180 kDa and comigrated with reduced platelet **thrombospondin** on NaDodSO4/PAGE. Immunoblot analysis with monospecific anti-**thrombospondin** confirmed the presence of immunoreactive **thrombospondin**. Indirect immunofluorescence of cultured human glial cells indicated the presence of **thrombospondin**. Metabolic labeling of glial cell cultures with [35S]methionine followed by immunoprecipitation with monospecific anti-**thrombospondin** revealed synthesis of a 180-kDa polypeptide that comigrated with platelet **thrombospondin** on NaDodSO4/PAGE. Cultured human glial cells were incubated for 48 hr in serum-free medium with purified platelet-derived growth factor at concentrations up to 50 ng/ml. Aliquots taken at intervals were analyzed by a quantitative double-antibody ELISA. The growth factor stimulated the release of **thrombospondin** into the culture medium by as much as 10-fold over control cultures. The presence of **thrombospondin** within glial cells of the central nervous system and the augmentation of its synthesis by platelet-derived growth factor suggest that **thrombospondin** may play an important role in regulating cell-cell and cell-matrix interactions during periods of cell division and growth.

L6 ANSWER 23 OF 32 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 86272791 MEDLINE
DOCUMENT NUMBER: 86272791 PubMed ID: 2942332
TITLE: Advances in clinical fibrinolysis.
AUTHOR: Hessel L W; Kluft C

SOURCE: CLINICS IN HAEMATOLOGY, (1986 May) 15 (2) 443-63.
Journal code: DE7; 0331547. ISSN: 0308-2261.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198609
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19980206
Entered Medline: 19860916

AB The discovery of a fast-acting plasminogen activator inhibitor has resulted in the notion that the balance between tissue-type plasminogen activator and its inhibitor determines the net fibrinolytic activity of blood. The inhibitor shows a rapidly fluctuating acute-phase pattern, which may be important in relation to thrombosis in acute disease. Other newly discovered modulators of the fibrinolytic system include **histidine-rich glycoprotein**, tetranectin and **thrombospondin**. The role of fibrin as a cofactor in its own dissolution is further elucidated with emphasis on local aspects. Therapeutic inhibition of overactive fibrinolysis by various drugs needs careful monitoring. Prophylactic stimulation of fibrinolysis is possible, e.g. by stanozolol or other drugs that lower inhibitor levels, but its proven value is as yet limited. Results of clinical trials with activators of the fibrinolytic system as thrombolytic agents are discussed in relation to the physiology of the fibrinolytic system.

L6 ANSWER 24 OF 32 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 85261463 MEDLINE
DOCUMENT NUMBER: 85261463 PubMed ID: 3160707
TITLE: Activation of immobilized plasminogen by tissue activator. Multimolecular complex formation.
AUTHOR: Silverstein R L; Nachman R L; Leung L L; Harpel P C
CONTRACT NUMBER: HL18828 (NHLBI)
HL30649 (NHLBI)
K11HLAM1442 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1985 Aug 25) 260 (18) 10346-52.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198509
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19850925

AB Ternary complex formation of tissue plasminogen activator (TPA) and

plasminogen (Plg) with **thrombospondin** (TSP) or **histidine-rich glycoprotein** (**HRGP**) has been demonstrated using an enzyme-linked immunosorbent assay, an affinity bead assay, and a rocket immunoelectrophoresis assay. The formation of these complexes was specific, concentration dependent, saturable, lysine binding site-dependent, and inhibitable by fluid phase plasminogen. Apparent Kd values were approximately 12-36 nM for the interaction of TPA with TSP-Plg complexes and 15-31 nM with **HRGP**-Plg complexes. At saturation the relative molar stoichiometry of Plg:TPA was 3:1 within the TSP-containing complexes and 1:1 within **HRGP**-containing complexes. The activation of Plg to plasmin by TPA on TSP- and **HRGP**-coated surfaces was studied using a synthetic fluorometric plasmin substrate (D-Val-Leu-Lys-7-amino-4-trifluoromethyl coumarin). Kinetic analysis demonstrated a marked increase in the affinity of TPA for plasminogen in the presence of surface-associated TSP or **HRGP**. Compared to fluid phase activation or activation on fibronectin- or Factor VIII-related antigen-coated surfaces there was a 35-fold increase in efficiency of plasmin generation. A substantial amount (up to 71%) of the plasmin formed remained surface-associated and was found to be protected from inhibition by alpha 2-plasmin inhibitor. Greater than 200-fold increase in inhibitor concentration was required to effect 50% inhibition. Complex formation of locally released tissue plasminogen activator with Plg immobilized on TSP or **HRGP** surfaces may thus play an important role in effecting proteolytic events in nonfibrin-containing microenvironments.

L6 ANSWER 25 OF 32 MEDLINE DUPLICATE 13

ACCESSION NUMBER: 85234931 MEDLINE
DOCUMENT NUMBER: 85234931 PubMed ID: 4008652
TITLE: Platelet **thrombospondin** forms a trimolecular complex with plasminogen and **histidine-rich glycoprotein**
AUTHOR: Silverstein R L; Leung L L; Harpel P C; Nachman R L
CONTRACT NUMBER: HL18828 (NHLBI)
K11HLAM1442 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1985 Jun) 75 (6) 2065-73.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198507
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19980206

Entered Medline: 19850730

AB **Thrombospondin** (TSP), a multifunctional alpha-granule glycoprotein of human platelets binds fibrinogen, fibronectin, heparin, **histidine-rich glycoprotein** (**HRGP**), and plasminogen (Plg), and thus, may play an important role in regulating thrombotic influences at vessel surfaces. In this study we have demonstrated that purified human platelet TSP formed a trimolecular complex with human Plg and **HRGP**. Complex formation was detected by a specific binding enzyme-linked immunosorbent assay (ELISA) which demonstrated simultaneous binding of fluid-phase Plg and **HRGP** to TSP adsorbed to microtitration wells. While neither ligand inhibited complex formation of the other with TSP, 10 mM epsilon-amino-n-caproic acid selectively blocked incorporation of Plg into the complex, suggesting that TSP contains independent binding sites for Plg and **HRGP**. Comparable extent of trimolecular complex formation was also detected when TSP monomer was substituted for whole TSP in the ELISA. **HRGP** covalently cross-linked to Sepharose 4B simultaneously bound both 125I-TSP and 131I-Plg, confirming trimolecular complex formation. Rocket immunoelectrophoresis of mixtures of the purified radiolabeled proteins into anti-Plg containing agarose also confirmed trimolecular complex formation. The TSP-**HRGP**-Plg complex bound a similar amount of heparin as the TSP-**HRGP** complex, demonstrating that the **HRGP** within the trimolecular complex maintained functional capability. Similarly, using a fluorometric plasmin substrate, the trimolecular complex was shown to be an effective substrate for tissue plasminogen activator. Significant amounts of plasmin were generated from the TSP-**HRGP**-Plg complex (equivalent to that from the TSP-Plg complex), but the rate of plasmin generation from the trimolecular complex was greater than from the bimolecular complex, suggesting an important interaction of **HRGP** with Plg when both are complexed to TSP. The macromolecular assembly of these three proteins on cellular surfaces, such as the platelet, may serve important regulatory functions, both prothrombotic at sites of active fibrin deposition and proteolytic in nonfibrin-containing microenvironments.

L6 ANSWER 26 OF 32 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1985:180299 BIOSIS
DOCUMENT NUMBER: BR29:70295
TITLE: **THROMBOSPONDIN** FORMS A SURFACE FOR PLASMINOGEN ACTIVATION BY TISSUE ACTIVATOR FORMATION OF A TERNARY COMPLEX.
AUTHOR(S): SILVERSTEIN R L; LEUNG L L K; HARPEL P C; NACHMAN R L
CORPORATE SOURCE: CORNELL UNIV. MED. COLL., NEW YORK, N.Y.
SOURCE: 42ND ANNUAL NATIONAL MEETING OF THE AMERICAN

FEDERATION FOR CLINICAL RESEARCH, WASHINGTON, D.C., USA, MAY 3-6, 1985. CLIN RES, (1985) 33 (2 PART 1), 353A.
CODEN: CLREAS. ISSN: 0009-9279.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L6 ANSWER 27 OF 32 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1985:106606 BIOSIS
DOCUMENT NUMBER: BR28:106606
TITLE: LOW-SPIN TO HIGH-SPIN CONVERSION OF HEME BOUND TO **HISTIDINE-RICH GLYCOPROTEIN**
.
AUTHOR(S): BURCH M K; MORGAN W T
CORPORATE SOURCE: DEP. BIOCHEM., LA. STATE UNIV. MED. CENT., NEW ORLEANS, LA 70112, USA.
SOURCE: 29TH ANNUAL MEETING OF THE BIOPHYSICAL SOCIETY, BALTIMORE, MD., USA, FEB. 24-28, 1985. BIOPHYS J, (1985) 47 (2 PART 2), 83A.
CODEN: BIOJAU. ISSN: 0006-3495.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L6 ANSWER 28 OF 32 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 85055474 MEDLINE
DOCUMENT NUMBER: 85055474 PubMed ID: 6438154
TITLE: Complex formation of platelet **thrombospondin** with plasminogen. Modulation of activation by tissue activator.
AUTHOR: Silverstein R L; Leung L L; Harpel P C; Nachman R L
CONTRACT NUMBER: HL18828 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1984 Nov) 74 (5) 1625-33.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198412
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19980206
Entered Medline: 19841224
AB **Thrombospondin** (TSP), a multifunctional alpha-granule glycoprotein of platelets, binds fibrinogen, fibronectin, heparin, and **histidine-rich glycoprotein** and thus may play an important role in regulating thrombotic influences

at vessel surfaces. In this study we have demonstrated that purified human platelet TSP formed a complex with purified human plasminogen (Plg). Complex formation was detected by rocket immunoelectrophoresis of mixtures of the purified radiolabeled proteins. Significant complex formation of fluid-phase Plg with adsorbed TSP was also demonstrated by enzyme-linked immunosorbent assay (ELISA). The complex formation was specific, saturable, and inhibited by excess fluid-phase TSP, with an apparent KD of approximately 35 nM. In both ELISA and rocket immunoelectrophoresis systems, complex formation was inhibited by 10 mM epsilon-amino-n-caproic acid, implying that there is a role for the lysine binding sites of Plg in mediating the interaction. TSP also formed a complex with plasmin as detected by ELISA but did not directly inhibit plasmin activity measured with a synthetic fluorometric substrate or with a 125I-fibrin plate assay. TSP, when incubated with Plg before addition to 125I-fibrin plates significantly inhibited the generation of plasmin activity by tissue plasminogen activator (TPA) in a manner that was calcium dependent. A kinetic study of Plg activation by TPA in the presence of TSP demonstrated that Michaelis-Menten kinetics were followed and that TSP acted as a noncompetitive inhibitor. These studies support the hypothesis that TSP, acting as a multifunctional regulator in focal areas of active hemostasis, could serve as a prothrombotic influence, leading to increased deposition of fibrin.

L6 ANSWER 29 OF 32 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 84088293 MEDLINE
DOCUMENT NUMBER: 84088293 PubMed ID: 6690483
TITLE: Complex formation of platelet **thrombospondin** with **histidine-rich glycoprotein**.
AUTHOR: Leung L L; Nachman R L; Harpel P C
CONTRACT NUMBER: HL 18828 (NHLBI)
K08 HL00877 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1984 Jan) 73 (1) 5-12.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198402
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19980206
Entered Medline: 19840220

AB **Thrombospondin** and **histidine-rich glycoprotein** are two proteins with diverse biological activities which have been associated with human platelets and other

ascites (15 cases) and group of haematemesis (15 cases): in addition to a normal control group (15 subjects). The physiological inhibitors of fibrinolysis included in this study were protease inhibitors (plasminogen activator inhibitor, alpha 2 antiplasmin, antithrombin III, heparin cofactor II and Cl- inactivator). Other proteins regulating fibrinolysis (**histidine rich glycoprotein**, protein C and **thrombospondin**) were estimated in all groups in a trial to clarify their role in haemostasis in hepatosplenic schistosomiasis. Euglobulin clot lysis time was performed as a screening test and its progressive shortening confirmed the existence of accelerated fibrinolysis. The data obtained revealed significant progressive decrease in all parameters studied (except **thrombospondin**) with advancement of the disease, especially in advanced fibrotic and haematemesis groups. This could be due to the decreased synthesis due to hepatocellular failure and/or increased consumption of physiological inhibitors of fibrinolysis. On the other hand, **thrombospondin** showed significant progressive increase parallel to the progress of the disease; this may be explained by its extraplatelet sources mainly the vascular endothelium or its longer life span. These data confirm the enhancement of fibrinolytic activity as the disease progressed. It could be concluded that the accelerated fibrinolytic activity reported in late stages of the disease may be one of the direct causes of haemorrhagic diathesis in hepatosplenic schistosomiasis.

L6 ANSWER 31 OF 32 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:359981 BIOSIS
DOCUMENT NUMBER: PREV199699082337
TITLE: Physiological inhibitors of coagulation and fibrinolysis before and after sclerotherapy in chronic liver disease.
AUTHOR(S): Toima, Salwa M.; Essawy, Faiza M.; Mostafa, I. M.; Omran, Sawsan A. (1)
CORPORATE SOURCE: (1) Haematol. Dep., Theodor Bilharz Res. Inst., Imbaba, PO Box 30, Guiza Egypt
SOURCE: Egyptian Journal of Bilharziasis, Vol. 15, No. 1-2, pp. 49-59.
ISSN: 0301-8849.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English; Arabic
AB This work was carried out on twenty nine patients with grade IV oesophageal varices. Patients under study were treated with endoscopic injection sclerotherapy (EIS), using two sclerosant materials. Ethanolamine oleate (EO) 5% was used in nineteen patients, and polidocanol (PD) 1% was used in ten patients. Comparative evaluation of their impact on the physiological

inhibitors of both coagulation and fibrinolytic systems was done. We studied the effect of sclerotherapy on selected haemostasis by estimating prothrombin time (PT), partial thromboplastin time (PTT) and thrombin time (TT) together with plasminogen and fibrinogen. The physiological inhibitors of coagulation and fibrinolysis included in this study were antithrombin III, C1-inactivator, infin -2 antiplasmin, heparin cofactor II, protein C, **histidine rich glycoprotein** and **thrombospondin**.
Following EIS with EO, almost all patients had significant decreased level of PT, PTT, TT, plasminogen and fibrinogen, as well as a decrease in all physiological inhibitors studied. On the other hand, significant decreases were detected only in antithrombin III, infin -2-antiplasmin and plasminogen in patients treated by PD injection. These data indicate that EIS resulted in a transient activation of the clotting system with a mild consumptive coagulopathy which in turn lead to decreased levels of the physiological inhibitors. Also EO was more effective than PD and had fewer complications.

L6 ANSWER 32 OF 32 CONFSCI COPYRIGHT 2001 CSA
ACCESSION NUMBER: 82:53987 CONFSCI
DOCUMENT NUMBER: 83007644
TITLE: Complex formation of platelet **thrombospondin** with **histidine-rich glycoprotein**
AUTHOR: Leung, L.L.K.; Nachman, R.L.; Harpel, P.C.
CORPORATE SOURCE: Cornell Univ. Med. Coll., New York, NY, USA
SOURCE: Abstracts in: "Blood - The Journal of the American Society of Hematology", Nov. 1982, Grune & Stratton, Inc., 111 Fifth Ave., New York, NY 10003, USA, ISSN 0006-4971.
Meeting Info.: 824 5015: American Society of Hematology, 24th Annual Meeting (8245015). Washington , DC. 4-7 Dec 82. American Society of Hematology.
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L8 0 S L7 NOT L4

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L9 21 S L7
L10 0 S L9 NOT L5

FILE 'CAPLUS' ENTERED AT 10:06:47 ON 21 JUN 2001
L11 0 S L3 AND GMP

FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 10:07:37 ON 21 JUN 2001

L12 0 S L11

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